EXHIBIT F

Designation: F 1980 – 02

Standard Guide for Accelerated Aging of Sterile Medical Device Packages[1]

This standard is issued under the fixed designation F 1980; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

1. Scope

1.1 This guide provides information for developing accelerated aging protocols to rapidly determine the effects, if any, due to the passage of time and environmental effects on the sterile integrity of packages and the physical properties of their component packaging materials.

1.2 Information obtained using this guide may be used to support expiration date claims for medical device packages.

1.3 The accelerated aging guideline addresses the primary medical package in whole and does not address the package and product interaction or compatibility that may be required for new product development. Package and product compatibility and interactions should be addressed as a material analysis process before package design.

1.4 Real-time aging protocols are not addressed in this guide; however, it is essential that real-time aging studies be performed to confirm the accelerated aging test results using the same methods of evaluation.

1.5 Methods used for package process validation, which include the machine process, the effects of the sterilization process, distribution, handling, and shipping events, are beyond the scope of this guide.

1.6 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety and health practices and determine the applicability of regulatory limitations prior to use.*

2. Referenced Documents

2.1 *ASTM Standards:*

D 3078 Test Method for Determination of Leaks in Flexible Packaging by Bubble Emission[2]

D 4169 Practice for Performance Testing of Shipping Containers and Systems[2]

D 4332 Practice for Conditioning Containers, Packages, or Packaging Components for Testing[2]

E 337 Test Method for Measuring Humidity with a Psychrometer (The Measurement of Wet- and Dry-Bulb Temperatures[3]

F 88 Test Method for Seal Strength of Flexible Barrier Materials[2]

F 1140 Test Methods for Failure Resistance of Unrestrained and Nonrigid Packages for Medical Applications[2]

F 1327 Terminology Relating to Barrier Materials for Medical Packaging[2]

F 1585 Guide for Integrity Testing of Porous Barrier Medical Packages[2]

F 1608 Test Method for Microbial Ranking of Porous Packaging Materials (Exposure Chamber Method)[2]

F 1929 Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration[2]

2.2 *AAMI Standards:*

ANSI/AAMI/ISO 11607, Packaging for Terminally Sterilized Medical Devices[4]

AAMI TIR 17-1997, Radiation Sterilization—Material Qualification[4]

3. Terminology

3.1 *Definitions*—For general definitions of packaging for medical devices see ANSI/AAMI/ISO 11607. For terminology related to barrier materials for medical packaging see Terminology F 1327.

3.2 *Definitions of Terms Specific to This Standard:*

3.2.1 *accelerated aging (AA), n*—storage of samples at an elevated temperature (T_{AA}) in order to simulate real time aging in a reduced amount of time.

3.2.2 *accelerated aging factor (AAF), n*—an estimated or calculated ratio of the time to achieve the same level of physical property change as a package stored at real time (*RT*) conditions.

3.2.3 *accelerated aging temperature (T_{AA}), n*—the elevated temperature at which the aging study is conducted, and it may be based on the estimated storage temperature, estimated usage temperature, or both.

3.2.4 *accelerated aging time (AAT), n*—the length of time the accelerated aging is conducted.

3.2.5 *ambient temperature (T_{RT}), n*—storage temperature

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[2] *Annual Book of ASTM Standards*, Vol 15.09.

[3] *Annual Book of ASTM Standards*, Vol 11.03.

[4] Available from the American National Standards Institute, 25 W. 43rd St., 4th Floor, New York, NY 10036.

for real-time aging (*RT*) samples that represents storage conditions.

3.2.6 *package shelf life*, *n*—the amount of real time that a package can be expected to remain in storage at ambient conditions, or under specified conditions of storage, and maintain its critical performance properties.

3.2.7 *real-time aging (RT)*, *n*—storage time of samples at ambient conditions.

3.2.8 *real-time equivalent (RTE)*, *n*—amount of real-time aging to which given accelerated aging conditions are estimated to be equivalent.

3.2.9 *zero time* (t_0), *n*—the beginning of an aging study.

3.3 *Symbols:*

Q_{10} = an aging factor for 10°C increase or decrease in temperature.
T_m = temperature at which a material melts.
T_g = glass transition temperature.
T_α = alpha temperature; heat distortion temperature.

4. Significance and Use

4.1 The loss of package integrity may occur as a result of physical properties of the materials and adhesive or cohesive bonds degrading over time and by subsequent dynamic events during shipping and handling.

4.2 The ANSI/AAMI/ISO 11607 states that, "the manufacturer shall demonstrate that, under the rigors of distribution, storage, handling, and aging, the integrity of the final package is maintained at least for the claimed shelf-life of the medical device under storage conditions specified by the manufacturer, as long as the package is undamaged or unopened."

4.3 Real time aging programs provide the best data to ensure that package materials and package integrity do not degrade over time. However, due to market conditions in which products become obsolete in a short time, and the need to get new products to market in the shortest possible time, real time aging studies do not meet this objective. Accelerated aging studies provide an alternative means. To ensure that accelerated aging studies do truly represent real time effects, real time aging studies must be conducted in parallel to accelerated studies. Real time studies must be carried out to the claimed shelf life of the product.

4.4 Conservative accelerated aging factors (AAFs) must be used if little is known about the package material being evaluated. More aggressive AAFs may be used with documented evidence to show a correlation between real time and accelerated aging.

NOTE 1—Determining AAFs are beyond the scope of this guide.

5. Apparatus

5.1 *Room (or Cabinet)* of such size that sample containers or packages may be individually exposed to circulating air at the temperature and relative humidity chosen.

5.1.1 *Control Apparatus*, capable of maintaining the room at the required atmospheric conditions within the tolerance limits.

5.2 *Hygrometer*—The instrument used to indicate the relative humidity should be accurate to ±2 % relative humidity. A psychrometer may be used either for direct measurement of relative humidity or for checking the hygrometer (see Test Method E 337).

5.3 *Thermometer*—Any temperature-measuring device may be used provided it can accurately indicate the temperature to within 0.1°C or 0.2°F. The dry-bulb thermometer of the psychrometer may be used either for direct measurement or for checking the temperature-indicating device.

6. Accelerated Aging Theory

6.1 Accelerated aging of materials refers to the accelerated variation of their properties over time, the properties of interest being those related to safety and function of the material or package.

6.2 In an aging study, the material or package is subjected to an external stress, which is more severe, or more frequently applied than the normal environmental stress, for a relatively short period of time.

6.3 Accelerated aging techniques are based on the assumption that the chemical reactions involved in the deterioration of materials follow the Arrhenius reaction rate function. This function states that a 10°C increase or decrease in temperature of a homogeneous process results in approximately, a two times or ½-time change in the rate of a chemical reaction (Q_{10})[5].

6.4 Determining the Q_{10} involves testing products at various temperatures and defining the differences in reaction rate for a 10° change in temperature. Modeling the kinetics of material deterioration is complex and difficult and is beyond the scope of this guide.[6]

7. Accelerated Aging Plan

7.1 *Characterization of Materials*—AA theory and its application are directly related to packaging material composition. Some areas for consideration are:

7.1.1 Composition,

7.1.2 Morphology (glassy, amorphous, semi-crystalline, highly crystalline, % crystallinity, etc.),

7.1.3 Thermal transitions (T_m, T_g, T_α),

7.1.4 Additives, processing agents, catalysts, lubricants, residual solvents, and fillers.

7.2 *Accelerated Aging Plan-Design Guidelines*:

7.2.1 Temperature boundaries, based on the characterization of the device and package materials, must be considered in order to ensure that initial, conservative aging factors are applied appropriately. The temperatures used should be based on the characterization of the packaging materials and the intended storage conditions. Material characterization and composition are factors in establishing the accelerated aging temperature boundaries. Temperature selection should be limited to prevent any physical transition of material.

7.2.2 *Room or Ambient Temperature* (T_{RT})—Select a temperature that represents the actual product storage and use conditions.

[5] Hemmerich, Karl J., "General Aging Theory and Simplified Protocol for Accelerated Aging of Medical Devices," *Medical Plastics and Biomaterials*, July/August 1998, pp. 16–23.

[6] Nelson, Wayne, "Accelerated Testing Statistical Models, Test Plans, and Data Analyses." John Wiley and Sons, New York, 1999.

NOTE 2—This temperature is typically between 20–25°C. A temperature of 25°C is considered a conservative approach.

7.2.3 *Accelerated Aging Temperature (T_{AA})*—Considering the characterization of the materials under investigation, select a temperature for the accelerated aging testing. The higher the accelerated temperature, the greater the AAF and, thus, the shorter the accelerated aging time. Care must be taken not to elevate aging temperatures solely for the shortest possible accelerated aging time. Excessively high temperatures may have an effect on the material that may never occur during real time or at room temperature (see Appendix X1). Guidelines for selecting an aging temperature are as follows:

7.2.3.1 T_{AA} should be below any material transitions or below where the package distorts. Consider the thermal transitions of the materials under investigation, for example, the choice of T_{AA} should be at least 10°C less than T_g. (For more information on this topic, see AAMI TIR 17-1997.)

7.2.3.2 Keep T_{AA} at or below 60°C unless a higher temperature has been demonstrated to be appropriate. Temperatures higher than 60°C are not recommended due to the higher probability in many polymeric systems to experience nonlinear changes, such as percent crystallinity, formation of free radicals, and peroxide degradation. (For more information on this topic, see AAMI TIR 17-1997.)

NOTE 3—If packages containing liquid or other volatile components are tested, lower temperatures may be required for safety reasons.

7.2.3.3 When elevated temperature aging is not feasible due to material characteristics, then real-time aging is the only option.

7.3 *Accelerated Aging Factor (AAF) Determination*:

7.3.1 Using the Arrhenius equation with Q_{10} equal to 2 is a common and conservative means of calculating an aging factor.

NOTE 4—A more aggressive reaction rate coefficient, for example, Q_{10}= 2.2 to 2.5, may be used if the system under investigation is sufficiently well characterized in the literature. The level and nature of damage must be similar to that reported in the literature to ensure that the reaction rate coefficient and accelerated aging temperature are maintained within appropriate boundaries. This is the responsibility of the manufacturer. For more information on this topic see AAMI TIR-17-1997.

7.3.2 An accelerated aging factor (AAF) estimate is calculated by the following equation:

$$AAF \equiv Q_{10}^{[(T_{AA} - T_{RT})/10]} \quad (1)$$

where:

T_{AA} ≡ accelerated aging temperature (°C), and

T_{RT} ≡ ambient temperature (°C).

7.3.3 The accelerated aging time (AAT) needed to establish equivalence to real time aging is determined by dividing the desired (or required) shelf life by the AAF.

$$\text{Accelerated Aging Time (AAT)} \equiv \text{Desired (RT)/AAF} \quad (2)$$

See Appendix X1 for a graphical representation of the time versus temperature.

7.3.4 When little information is known about the package under investigation, the guidance above is provided for selecting and verifying an appropriately conservative aging factor for the specific scenario. Risk to the manufacturer may be large since the method may predict an unduly short shelf-life; however, consideration must be given to maximizing patient safety since the necessary information to obtain a more accurate and aggressive shelf-life prediction is not readily available.

7.4 *Accelerated Aging Protocol Steps*:

7.4.1 Select the Q_{10} value.

7.4.2 Define the desired shelf life of the package, such as, marketing needs, product needs, etc.

7.4.3 Define aging test time intervals, including time zero.

7.4.4 Define test conditions, room temperature (T_{RT}), and accelerated aging temperature (T_{AA}).

7.4.5 Calculate the test duration using the Q_{10}, T_{RT}, and T_{AA}.

7.4.6 Define package material properties, seal strength and integrity tests, sample sizes, and acceptance criteria.

7.4.7 Age samples at T_{AA}. In parallel, age samples at real-life aging conditions (T_{RT}).

7.4.8 Evaluate the package performance after accelerated aging relative to the initial package requirements, for example, package seal strength, package integrity.

7.4.9 Evaluate package, or package performance, or both, after real time aging relative to the initial package requirements. The estimated AAF method is a simple and conservative technique for evaluating the long-term performance of a package; however, like all accelerated aging techniques, it must be confirmed by real time aging data.

7.5 See the example package shelf-life test plan (Appendix X2).

8. Post-Aging Testing Guidance

8.1 Packages and materials that have been subjected to aging, that is, accelerated and real time, must be evaluated for physical properties and integrity.

8.2 Tests selected should challenge the material or package functionality that is most critical or most likely to fail due to the stresses resulting from aging. Guide F 1585 may be used as a testing guide for porous barrier medical packaging.

8.3 Some of the physical strength properties to be considered for selection are flexure, puncture, tensile and elongation, tear, impact resistance, abrasion resistance, yellowness index, microbial barrier (Test Method F 1608), seal strength (Test Method F 88), and burst strength (Test Methods F 1140).

8.4 Packages may be subjected to whole package integrity testing by using validated physical, that is, trace gas detection, dye leak (Test Method F 1929), bubble leak (Test Method D 3078) or microbial methods (microbial challenge of whole packages). These methods must include documentation showing that the test method has been validated.

8.5 Acceptance criteria must be established prior to any package shelf-life testing. Zero time performance data may be used as a comparison to final package performance data at the end of the shelf life test.

9. Documentation

9.1 *Accelerated Aging*:

9.1.1 A written test protocol specifying the accelerated aging conditions (test temperature, humidity, cycle, ambient temperature), time frame, sample sizes, package description, time intervals of sampling packages, and specific tests at each time interval must be developed prior to testing.

9.1.2 Document the temperature of the chamber used and the calibrated instruments used for measuring and monitoring the aging conditions.

9.1.3 Document the test standard references and methods used for package evaluation.

9.1.4 List the equipment used for physical and microbial testing including the calibration dates.

9.1.5 Document the post aging test results including, any statistical methods used to determine whether the package meets the performance specification criteria.

10. Keywords

10.1 accelerated aging; Arrhenius reaction rate; Q_{10}; shelf-life

APPENDIXES

(Nonmandatory Information)

X1. ACCELERATED AGING OF POLYMERS

X1.1 Accelerated aging (Fig. X1.1) equivalent to one year of room-temperature aging when the package is heat-aged at a selected temperature (°C).

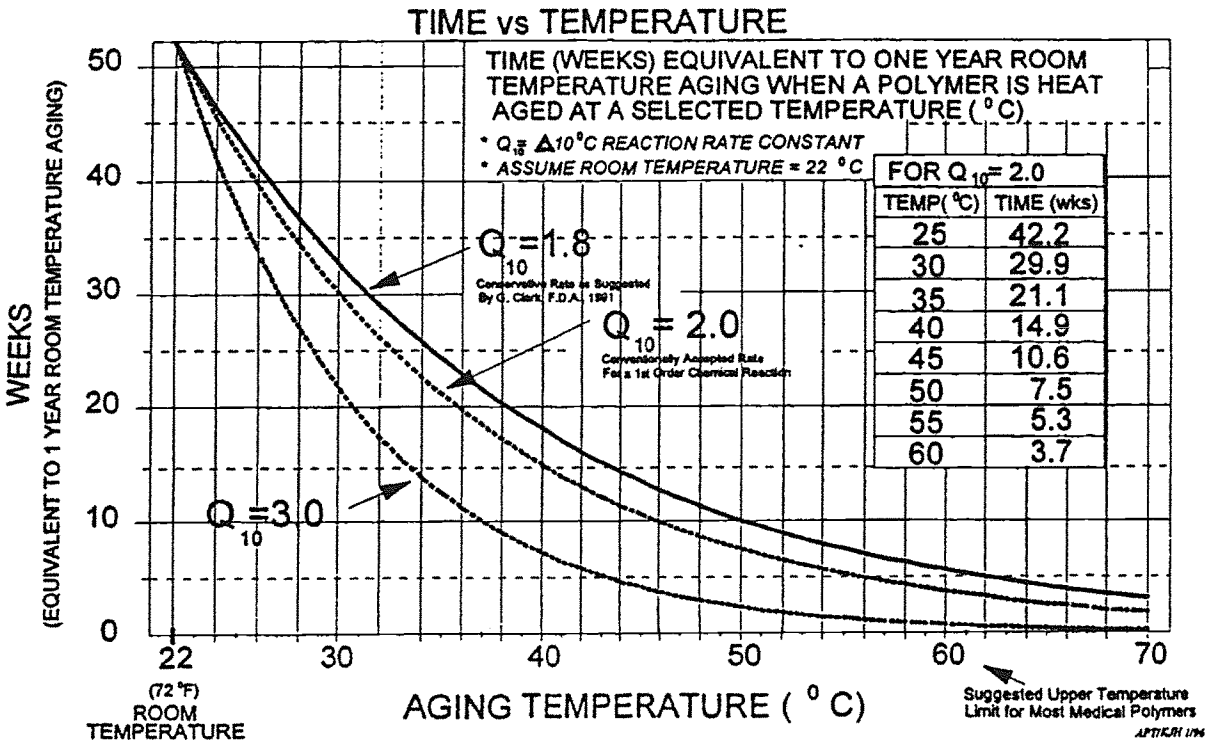

FIG. X1.1 Accelerated Aging of Polymers[5]

X2. EXAMPLE PACKAGE SHELF-LIFE TEST PLAN

X2.1 Select a conservative AAF estimate, for example, Q_{10} = 2. (See Fig. X2.1.)

X2.2 Define aging time points corresponding to the desired shelf life, for example, two points, such as 2-year and 3-year.

NOTE X2.1—Trending often is helpful when characterizing the aging effects on material and package properties. The number of accelerated aged time points, minimally, is one. The one mandatory time point is at the time equivalent to the desired shelf-life (desired shelf-life divided by aging factor); however, the practice of using only one accelerated time point leaves the risk of failure without prior warning from an earlier accelerated aged time point. At least three time points should be considered when trending.

X2.3 Build test samples in accordance with a validated production process.

NOTE X2.2—Packages used for zero-time, sterilization, and accelerated aging may be produced without actual or simulated product.

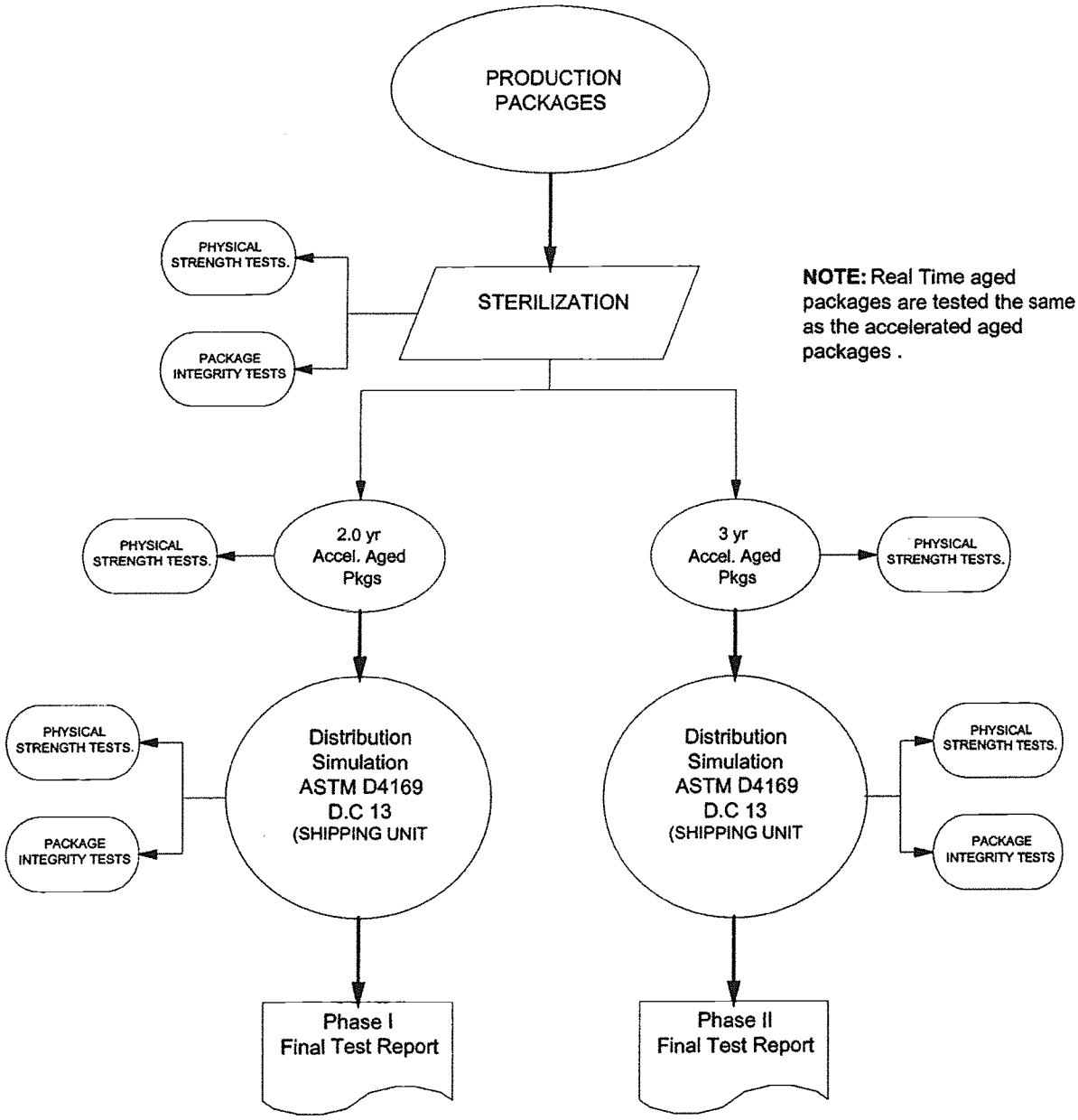

FIG. X2.1 Package Shelf-Life Test Plan

X2.4 Sterilize packages using validated sterilization process. The sterilization process may affect the stability of the materials or package. Materials and packages should be exposed to the maximum process conditions, or number of cycles intended to be used prior to the aging study, or both.

X2.5 Condition the samples according to Practice D 4332, if required; perform distribution simulation according to Practice D 4169, if appropriate. Packages used for this test must contain actual product.

NOTE X2.3—Package performance testing normally is performed as a part of the aging protocol to determine the long-term effects of distribution, handling, and storage. Whether performed before aging or after aging will depend on whether the study is to simulate storage on the hospital shelf or on the manufacturer's shelf and then shipped. There may be instances, however, where this may not be necessary. If known package failure or performance limits, such as seal strength, puncture, or impact resistance, etc., have been documented adequately and met for the specific intended product, then physical testing data should be sufficient.

X2.6 Initiate real-time and accelerated aging. Use the defined accelerated aging temperature for the appropriate period of time. The time duration for samples to be placed in the elevated temperature oven can be calculated from Eq 1 and 2 in 7.3.2 and 7.3.3, where AAF is the accelerated aging factor and AAT is the accelerated aging time.

For example, where Q_{10} = 2; ambient temperature = 23°C; test temperature = 55°C;

$AAF = 2.0^{(55-23)/10}$;
$AAF = 2.0^{3.2} = 9.19$;
AAT = 365 days/9.19; and
AAT ≡ 39.7 days ≡ 12 months (real-time equivalent).

NOTE X2.4—The effects of humidity may need to be considered in conjunction with temperature and incorporated into a test cycle of high and low humidity duration's. An aging cycle may be designed to account for the effects of humidity.

X2.7 Evaluate package performance after accelerated aging relative to the package requirements.

X2.7.1 If the accelerated aging results meet the acceptance criteria then the product's shelf-life conditionally is validated depending upon the results of the real-time aging study.

X2.7.2 If the accelerated aging results fail to meet the acceptance criteria then either investigate the production process, redesign the failed medical device or package, attempt to validate a shorter shelf-life, or wait for real time aging results. The shelf-life is validated if real time aging results are acceptable. In this scenario, the accelerated aging program is more rigorous than reality.

X2.8 Evaluate package performance after real-time aging relative to the package requirements.

X2.8.1 If the real-time aging results meet the acceptance criteria, then the package's shelf-life is validated.

X2.8.2 If the real-time aging results fail to meet the acceptance criteria, the shelf-life must be reduced to the longest shelf life for which real time testing has been successful. If product has been released to the market at risk based on the accelerated aging data, a careful review must be performed and documented, and the appropriate action taken.